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THE HISTORICAL FOUNDATIONS OF BIONICS

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1.1 BIONICS PAST AND FUTURE

In 1973, Donaldson and Davis published a paper called "Microelectronic devices for surgical implantation" in which they listed neuroprostheses in use and under development: pacemakers for the heart (fixed-rate, atrial-triggered and demand), incontinence devices, visual prostheses, dorsal column stimulators and electromyogram (EMG)) telemeters[1]. The field of bionics was then very young, the idea of surgically implanting an electronic device was new and very few people had worked on the technical difficulties entailed. Only pacemakers were then commercial products and there were no regulations in force. Now, 40 years later, there are many more types of device, both in clinical use and under development. A number of these devices will be described in Chapters 7–9 and include implants for addressing sensory loss (e.g. hearing, sight, balance), disorders of the brain and the mind (e.g. epilepsy, migraine, chronic pain, depression), as well as brain-machine interfaces. Manufacturing these devices and going through the process of regulation is now a multi-billion dollar industry.

The year 2013 may be remembered as the year in which GlaxoSmithKline (GSK) announced that they were to invest in the development of neurobionic devices, which

[1]The phrenic nerve stimulator ("Diaphram Pacer") of Glenn *et al.* (1973) was described in the same year.

Neurobionics: The Biomedical Engineering of Neural Prostheses, First Edition.
Edited by Robert K. Shepherd.

they call *Electroceuticals* or *Bioelectronic Medicines*[2] (Famm *et al*. 2013; Birmingham *et al*. 2014). The notion is that these will interact with the visceral nerves that innervate the internal organs to treat specific diseases. These diseases are not normally thought of as neurological (e.g. inflammation), but nevertheless there is some neural control. The announcement by GSK shows that the company thinks that implanted devices may become an alternative to some drug treatments. The motivations for their development no doubt include the rising costs of new drugs, better targeting of the causes of disease, and the realisation that implants might treat some of the increasingly prevalent diseases that threaten to overwhelm healthcare budgets (obesity, diabetes). They cite an example as the recent trial of a treatment for rheumatoid arthritis by stimulation of the vagus nerve (Koopman 2012). Some of the new implants will require surgical techniques new to human surgery, for example the splitting of spinal nerve roots in continuity into many fine strands. Only time will tell whether this vision is realistic, but it shows the huge rise in confidence that implanted bionic devices may be practicable and important in future healthcare.

The first electrical device implanted into a patient was the cardiac pacemaker of Elmqvist (1958), so the field is now nearly 60 years old (Figure 1.1). While Chapters 7–9 will review some of the types of implant with respect to their clinical

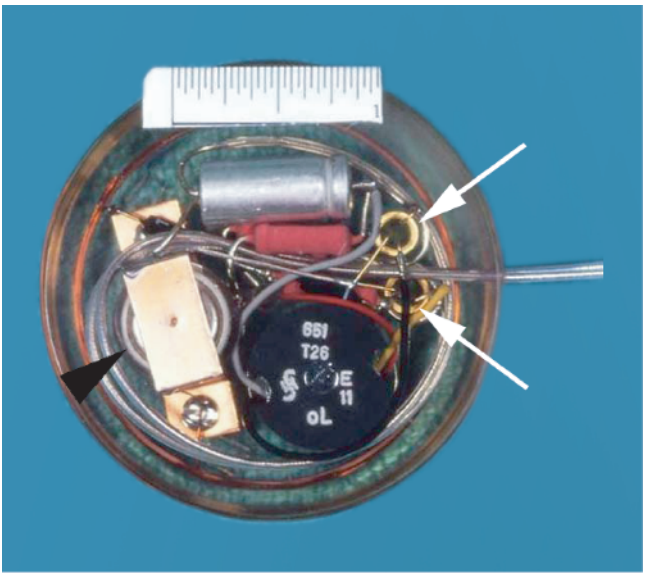


Figure 1.1 Elmqvist-Senning pacemaker of 1958. It is powered by two nickel-cadmium cells (arrowhead) which can be recharged by induction. The two transistors are on the right (arrows). The encapsulant is epoxy resin. An external valve oscillator was used for recharging at a frequency of 150 kHz. Scale bar = 1 inch.

[2]It will be interesting to see whether one of these names sticks, because both seem a misleading description of surgically-implanted devices.

function, Chapters 2–6 will review the field on which implant engineering is based, much of which has been built in this 60-year period. If we consider that the construction work in that period is the history of neurobionics, the purpose of this chapter is to look back to the pre-history, the foundation of the field, from the time before work began and probably before it was even conceived.

We have worked in London during the historical period (see Box 1.6: MRC Neurological Prostheses Unit) and the story is slanted toward our view of the significant technology.

1.2 HISTORY IN 1973

Donaldson and Davies (1973) suggested that neurological prostheses were the confluence of four streams of development: biomaterials (known from literature dating as far back as 1000 BC), electrical stimulation of nerves (Galvani 1791), electrophysiological recording (Matteucci 1842) and transistors (1948).

1.2.1 Biomaterials

A textbook by Susrata from 1000 BC describes the use of catgut for sutures. In Europe, from the 16th to the mid-19th century, linen and silk were the normal materials for sutures and ligatures; for sutures, horse hair, catgut and cotton were tried occasionally, and for ligatures, strips of leather. But these seem to have been passing fashions, and most surgeons continued to use silk or linen. Whatever the material, it was not a biomaterial in the modern sense; it was not expected to remain in the body for years, but either to be removed by the surgeon within a week or two, or to be extruded through the skin as part of the healing process within a few months.

The first internal fixation of a fracture with a metal plate and screws was performed by Lane in 1895, but Lane's plate and screws were of ordinary steel, and would certainly corrode. Stainless steel (*18-8* 18% chromium, 8% nickel) was patented in 1912, but the original stainless steel corroded badly in sea-water. It was not until about 1926 that a modified stainless steel, *18-8-SMo*, which had an additional 2–4% of molybdenum was developed, which resisted corrosion in sea-water and so could reasonably be expected to remain uncorroded in the body. This stainless steel was widely used in the internal fixation of fractures in the 1930s, and sometimes remained uncorroded for years (Haase 1937).

The variability remained mysterious, but it was made unimportant by the invention (1932) and introduction into bone surgery (1937) of Vitallium, an alloy of cobalt, chromium and molybdenum, which has never been reported as corroding in the body (Venable and Stuck (1938). The first widely successful artificial hip (though not absolutely the first artificial hip) was the cup arthroplasty (Smith-Peterson 1939). It used a *Vitallium* cup which was not bonded either to the head of the femur or to the acetabulum. Modern artificial hips have a ball bonded to the femur and a cup bonded to the pelvis. Problems of fixing the ball and cup to the bones and of wear at the articulating surfaces have been largely overcome. For artificial finger joints, it has been possible

to avoid articulating surfaces by using adequately flexible silicones (Williams and Roaf 1973). Silicones were first used in medicine as coatings for syringe needles for reduced blood clotting (1946). In the same year, silicone rubbers were first used for surgical repairs and, in 1956, for the first hydrocephalus shunts (Colas and Curtis 2004). Thus by 1973 the field of biomaterials was established as a collaboration between surgeons, biologists and materials scientists, who had made progress by innovation with new materials, better designs and improved surgical techniques.

Less was known about implantable electrical materials: the first electrical implant in an animal was described by Louks (1933) and that was simply a coil, insulated with Collodion varnish, connected directly to electrodes; the experiments continued for 12 days. Clearly the idea that artificial materials can be implanted into the body was well established by 1973, but the specific difficulties of electrical devices were new.

1.2.2 Nerve stimulation and recording

It was established by Galvani in 1791 that nerves could be stimulated. The idea that nerves carried sensory messages to the brain and commands back to the muscles was stated in the 1st century AD by Galen, who argued for it against contrary opinions of some classical Greek authorities; he thought that the nerve signal was transmitted by fluid flow. However, when Leeuwenhoek looked at nerves in cross-section using his new microscope (1674), he was not convinced that there was any tubular structure to carry the fluid.

Newton wrote in 1678 about "a certain most subtle spirit which pervades and lies hid in all gross bodies, by the force and action of which … all sensation is excited and the members of animal bodies move at the command of the will, namely by the vibrations of this spirit, mutually propagated along the solid filaments of the nerves, from the outward organs of sense to the brain, and from the brain into the muscles." For the optic nerve, Newton repeated this opinion in his "Opticks" (Newton 1730): "Do not the rays of light in falling upon the bottom of the eye excite vibrations in the tunica retina? Which vibrations, being propagated along the solid fibres of the optic nerve, cause the sense of seeing?"

Since 1745, when the Leyden jar was invented, it was well known that electricity passing through human skin causes strong and often painful sensations. At least since 1738 (Swammerdam) it was known that if, in a preparation consisting of a frog's gastrocnemius muscle and sciatic nerve and little else, the nerve was pinched, contraction of the muscle followed immediately. Galvani (1791), using just such a preparation, showed that passing electricity from a frictional machine through the nerve had the same effect. He also did experiments using dissimilar metals, which he misinterpreted. Volta confirmed and extended Galvani's experiments, interpreted them correctly, and used them as the basis of his invention of the battery (1800), which quickly led to the discovery of the relation between electricity and magnetism, the work of Oersted, Ampere, Ohm and Faraday, and the great advances in electro-technology from which we all benefit today.

The action potential of the nerve was first detected by Matteucci (1842). The speed of conduction of the nerve message was measured by Helmholtz (1850) by

comparing, in frog nerve-muscle preparations, the difference in timing of the muscle contraction according to whether the near or the far end of the nerve was stimulated electrically. He found it to be about 20 m/sec. In 1856, Herrmann measured the speed of movement of the action potential directly, and found that it was the same as that of the message as measured by Helmholtz, thus making it almost certain that the action potential was a true sign of the message.

The time course of the action potential at any one point on the nerve was known only very roughly until the development of valve amplifiers during the First World War. Gasser and Newcomer (1921) were the first to apply such amplifiers to nerve action potentials, and to display them on a cathode-ray oscilloscope. During 1921–1930, Gasser and Erlanger, in a long series of papers in the *American Journal of Physiology*, described these techniques and others to elucidate the form of the action potential and the influence of fibre diameter and myelination on it and on the speed of conduction. It was already known, from theory and from observations made with older equipment, that if both recording electrodes were placed on an intact nerve, a biphasic action potential was found, the potential difference reversing as the active region moved from one electrode to the other. However, if the end of the nerve was crushed and one electrode placed on it, a nearly-monophasic response was found. Gasser and Erlanger, with amplification, cathode-ray oscilloscope, a limb nerve (ulnar) and one recording electrode on an intact nerve at least 20 cm from the stimulating electrodes and the other on the crushed end of the nerve, found a monophasic response when they used weak stimuli, but with strong stimuli it became polyphasic, the additional peaks coming later than the one that was already present with weak stimuli. By good arguments from the results of further exploration, taking into account what was already known about the anatomy of limb nerves, they concluded that their nerve contained fibres of many different diameters. The largest conducted fastest and were most electrically sensitive. Smaller fibres were slower and less sensitive. The speeds of conduction did not follow a Gaussian distribution; they were strongly grouped into five classes, called Aα, Aβ, Aγ, B and C, by Erlanger and Gasser (1930). It soon became clear that the C fibres were unmyelinated and the A and B fibres were myelinated.

From about 1910–1930, there was much interest in how the amplitude of a rectangular pulse just sufficient to stimulate a nerve, nerve fibre, muscle or muscle fibre, varied with the duration of that pulse. Such measurements could be (and were) made with great accuracy, and easily showed that long pulses favoured unmyelinated nerve fibres and skeletal and cardiac muscle fibres, and that short pulses favoured myelinated nerve fibres, which were the most sensitive even to long pulses (say 10–20 milliseconds), but immensely so to short pulses (<0.5 msec). These experiments added little to our understanding of how the nervous system works, but are useful to the designers of bionic devices.

In 1939, A.L. Hodgkin made two steps towards understanding the nature of the nerve impulse. First he proved what had been suspected before but never proved: that the fraction of the action current of one node of Ranvier that is conducted along the axoplasm to the next node of Ranvier in a vertebrate myelinated nerve fibre is sufficient to stimulate this (next) node. Then, in the same year, Hodgkin succeeded

in recording the action potential of the giant nerve fibre of the squid from an electrode inserted into the fibre. Further research was interrupted by the war, but in 1952 Hodgkin and A.F. Huxley used intracellular recording from squid giant fibres to establish a thorough understanding of the electrical and ionic basis of the nerve impulse.

In contrast to the purely electrical transmission within a nerve cell and its processes, transmission from one neurone to another, sometimes excitatory but sometimes inhibitory, is almost always carried out by means of chemical transmitters. There are at least 20 of these. A few were discovered in the 1930s, many more in the 1950s and 1960s, and there may still be a few unidentified. One transmitter may have different actions on different postsynaptic neurones. Often (perhaps always) these different actions depend on different receptor molecules.

Much of our knowledge of the function of structures in the brain comes from observations of the effects of lesions, occurring in disease or (less often) produced experimentally. Observations of the effects of disease have led to new neurophysiological knowledge almost only when followed by good postmortem examination of the brain.

It was widely (though not universally) believed throughout the first two-thirds of the 19th century that all parts of the cerebral cortex were alike in function, with the reservation (going back to Hippocrates) that the left hemisphere was more concerned with the right half of the body and the right hemisphere with the left half. Such "equipotentiality" within each hemisphere was not disproved until 1863, when Broca observed that lesions of one small area of the left hemisphere caused inability to speak, and in 1871, when Fritsch and Hitzig showed that electrical stimulation of different parts of the cerebral cortex caused movements of different parts of the contralateral half of the body.

The effects of electrical stimulation *within* the brain became known only when Horsley and Clarke (1908) designed their apparatus for stereotaxic surgery, which allowed the end of a probe to be accurately placed almost anywhere within the brain. The tip of the probe carried an electrode, so the brain structure in which it lay could be stimulated electrically, or electrical activity recorded from it, or a lesion of controlled size made in it by diathermy. The Horsley-Clarke apparatus, originally for the human brain, was soon adapted for use in experimental animals.

1.2.3 Transistors

The transistor was essential for pacemakers and in fact the first human pacemaker was made just after silicon transistors became available with their lower leakage current. However, inductively-powered stimulators with tuned coils and solid-state rectifiers, not requiring implanted transistors, could have been made earlier; such devices have been very valuable in the development of neuroprostheses because of their simplicity and reliability. For example, the first visual prosthesis did not use implanted transistors, and the inductively-powered sacral anterior root stimulator uses them only in external equipment, including the oscillators that provide the radio-frequency magnetic fields. However, the arrival of transistors in the 1950s clearly showed the possibility for future small low-powered electronic devices, small

enough to implant. This sense of anticipation was increased by the development of the integrated circuit (patented in 1959).

1.2.4 Conclusion

Before a new type of bionic device is implanted into a patient, an ethical committee must be convinced that there is a reasonable chance that it will be effective and the risks of implantation are not too great. In the case of nerve stimulators and neural signal amplifiers, understanding the mechanisms is bound to be helpful, so scientific knowledge from biophysics and neurophysiology, that line of scientific endeavour that included Galvani, is valuable. The transistor allowed the necessary miniaturisation. Regarding risk, it is essential to know that the materials implanted in the body are harmless and provoke no more than a mild response that does not jeopardize the device or the patient's health.

It was true that in 1973 medical bionics depended on progress in all these fields, biomaterials, nerve recording and stimulation, and transistors, but surely there were several other antecedents and even if some were not apparent at the time that Donaldson and Davies were writing, we should now acknowledge them as having been essential to the success of the field. These other historical antecedents are the subject of the following sections.

1.3 ANAESTHESIA

Two hundred years ago, the idea of implanting an artificial device into the body would surely have been regarded as at best fanciful and at worst a horror. Surgeons had a desperate job to do while the patient tried to endure the extreme pain and good surgeons were those who were quick; amputations might be completed in seconds but remained agonising. Pain-killing drugs had long been used, notably opium and mandrake, but these (especially mandrake) had undesirable side effects.

Given that surgery caused so much suffering, it is perhaps surprising that the use of anaesthesia by nitrous oxide, ether and chloroform in surgery came as late as it did. Humphrey Davy, the chemist, discovered the pain-killing effect of nitrous oxide – laughing gas – and used it on himself while having a tooth removed. This was part of his earliest work, published in 1800 (Routledge 1881). Subsequently, not only did he demonstrate the effects of this gas in lectures but other chemists did too. Faraday pointed out that ether had similar effects to nitrous oxide in 1818 (Routledge 1881). However, the method was not immediately tested by clinicians and it was not until the 1840s that two small-town Americans, Crawford Long (doctor) and Horace Wells (dentist), anaesthetised patients with ether and nitrous oxide respectively. Neither gained recognition for their achievement. In Britain, nothing was done until J.Y. Simpson, Professor of Midwifery at Edinburgh, started experimenting with chloroform, first on his mother's dog, then on his friends as an evening amusement, before starting to use it on his patients during childbirth.

Chloroform had been discovered in 1831. Despite the apparent alleviation of pain, there was considerable resistance from traditionalists to use of chloroform during childbirth. This was largely overcome by the intervention of Queen Victoria who was expecting her seventh child. She commanded Simpson to act as midwife and, after delivery, gave royal approval for chloroform. In America, the breakthrough in surgery occurred when the dentist Dr William Morton, who had started experimenting with Wells, anaesthetised a patient with ether who was about to have a tumour removed by Professor Warren, Chief Surgeon at the Massachusetts Hospital in Boston in 1846: the operation in front of many witnesses was completely convincing. The first use during surgery in Britain was an amputation done under chloroform by Mr Robert Liston in 1846 at University College Hospital. Since a process for synthesizing ether was discovered in 1540 (Routledge 1881), there appears to be no reason why this huge advance in surgery could not have been discovered 300 years earlier.

1.4 ASEPTIC SURGERY

Until past the middle of the 19th century, death rates from infection following major surgical operations were very high, and such operations were done only for very strong reasons. The death rates fell greatly with *antiseptic surgery* (carbolic acid spray), introduced by Joseph Lister in Glasgow in 1867, and much further still in the 1880s with the development of *aseptic surgery* in which everything that touched or might touch the patient was sterilized in advance by heat.

1.5 CLINICAL OBSERVATION AND EXPERIMENTS

It would be completely wrong to think that the medical application of electricity was waiting for neuroscientific theory before attempting the treatment of patients. During the 18th century, science and particularly electrical science was of great popular interest and the fact that muscle could be stimulated through the skin by electric shocks from the friction generators of the time, caused widespread interest in its possible curative effects. Therapy was offered by conscientious practitioners such as John Wesley, as well as charlatans (Fara 2002). For example, paralysed patients travelled long distances to be treated by Benjamin Franklin who treated them with strong shocks by discharging large Leyden jars, but generally this was regarded as only a temporary cure[3]. Treatment of this sort continued right through to the early 20th century. McNeal (1977) reported that almost every American doctor's consulting room in the late 19th century had at least one electrical machine. In 1919, St Bartholomew's

[3]With our modern understanding, we would expect that these people would have upper motor neuron damage and the shocks only demonstrated that the paralysed nerve and muscle was still capable of contraction.

Hospital in London had an Electrical Department with a Medical Officer in Charge who wrote a book in which he divided the medical applications of electricity into the categories of: electrochemical cauterisation (destruction by caustic solution at the cathode); iontophoresis for introducing drugs into the body; diathermy; galvanic acupuncture (pain relief); and treatment for paralysis (Cumberbatch 1929). The list of conditions that he claimed could be treated is very long, from acne and angina, via moles and sciatica, to warts and writer's cramp; the list includes many infectious diseases but no evidence of efficacy was presented. Lumping the treatment of such diverse conditions together under the electrical umbrella seems to have been abandoned after the Great War.

Bionic devices are based on a foundation of neuroscience, but neuroscience is far more than the results of animal experiments, such as nerve-muscle preparations; a very large part of it is accumulated clinical observation. For most parts of the brain, clinical observations provide more than half of what is known about their function; for example, without clinical observation we should have no knowledge whatsoever of what the cerebellum does, even if we knew all that we now know about its connections and its chemical transmitters. Insight into the development of some bionic devices has followed such clinical observation, or experiments done with the patients' consent during surgical procedures. Two examples are mentioned in Box 1.5. One is Gordon Holmes's mapping of the visual cortex during the First World War; clinical observations on brain-damaged soldiers, which came near to being also an experiment, in that Holmes knew all that was already known about anatomical investigations of the geniculo-striate tract, and almost certainly adjusted the details of his examination of each patient so as to make each patient yield the greatest possible amount of information about the projection of the retina on the striate cortex. The second, also mentioned in Box 1.5, is the stimulation of the visual cortex during surgical removal of an epileptic focus from one occipital lobe; this was done by Foerster (1929) and by Krause and Schum (1931) a few years later. Stimulating electrically was not normal practice, and probably did not influence how much brain was removed. Both surgeons were experimenting, doing something that was very unlikely to cause harm and from which they were likely to learn something new. In fact, all these observations led to the idea of stimulating the visual cortex to give sight to the blind. Another example is the treatment of Parkinsonian patients by Deep Brain Stimulation. This derived from a chance clinical observation that a person, who had administered himself an illicit drug, methyl phenyl tetrahydropyridine (MPTP), developed symptoms like Parkinsonism (1983). The poison was administered to animals, which also developed the symptoms, and could be used as models. It was found that lesions in the sub-thalamic nucleus could reverse the symptoms (1990), and in 1993 treatment by stimulation of the nucleus had been demonstrated in patients (Limousin *et al*. 1995; see also Box 1.1).

Box 1.1 The treatment of pain

Suffering pain was always the lot of man and pain treatment is a topic in some of the earliest texts, such as the Egyptian papyri and clay tablets of Babylon. It was known from these early times that electric fish could provide relief by numbing the area affected: a Nile Catfish is shown in a tomb picture from the Egyptian 5th Dynasty (Kellaway 1946). Aristotle and others refer to the numbness produced by the shocks from these fish and the Roman writer Scribonius Largus (46 AD) described a treatment for headache. "Headache … is taken away … by a live black torpedo placed on the spot which is in pain, until the pain ceases. As soon as the numbness is felt, the remedy should be removed lest the ability to feel is taken from that part." (Rawlings *et al*. 1992).

The therapeutic use of electric fish continued and perhaps still continues, but after the invention of the friction electrostatic generator and the Leyden jar in 1745, the similarity between the two types of shock was clear. However, it was difficult to understand how this shock could be delivered under water, so Henry Cavendish (the man who discovered hydrogen and measured the weight of the Earth with a torsion balance) made an underwater model of the Torpedo fish that, while connected to a friction electrostatic generator, was able to give powerful shocks to peripheral nerves and induce numbness in those who came to see the demonstration (Fara 2002). In the 19th century, Duchenne treated neuralgia, sciatica and rheumatism by electricity; and after 1858, electro-anaesthesia was used in dentistry, the current being passed through the region of the affected tooth. By about 1870, a body of literature had been published (Rawlings *et al*. 1992), but the method then went into decline until it was rediscovered in about 1930 and after that a more scientific approach was taken with studies of dermatomes and physiological pathways, in particular by stimulation of the spinothalamic tract, the brainstem and the thalamus for pain relief. In 1965, Melzack and Wall published their *gate theory* of pain, which provided rationales for peripheral nerve and brain stimulation treatment (Melzack 1973). The first implants for treating chronic pain (dorsal column stimulators) were described by Sweet and Wepsic (1968).

There are now many different implant treatments for pain (Sakas *et al*. 2007), including: trigeminal nerve stimulation for craniofacial pain; occipital nerve stimulation for migraine; epidural stimulation of motor cortex for deafferentation pain; spinal cord stimulation for pains of the back; phantom limb and others types; and deep brain stimulation for many types of pain including spinal cord injury and peripheral neuropathies. Sakas *et al.* (2007) comment that management of chronic pain has been the greatest success of the neuromodulation treatments. Neuromodulation is an important addition to the treatment of pain by tissue ablation, neurotomy or drug delivery treatments, which are available to neurosurgeons. It is interesting that a significant step toward deep brain stimulation was an observation by Pool (1954) of an analgesic effect of stimulating the forniceal columns while carrying out psychosurgery, an effect that Pool and Heath found they could repeat in non-psychiatric patients (Raslan *et al.* 2007).

Box 1.2 The conventional implanted device since 1970

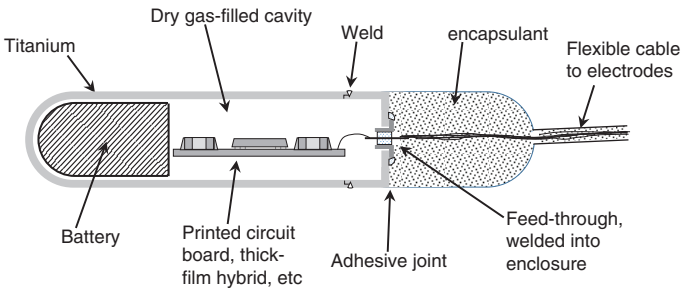


Figure Box 2 A non-scale drawing showing the main features of the most common type of implant during the last 40 years. The electronic components, and sometimes a battery are inside a metal enclosure which is "hermetic", meaning that leak rate of moisture is low enough that the inside will remain dry for the required lifetime of the device. Conductors are brought out through annular "feed-throughs", which comprise a metal pin, a glass or ceramic bush and a metal ring. On the outside of the enclosure, wires are joined to the pins of the feed-thoughs which may be part of the output cable (as shown) or may go to a surgical connector. The cables are usually either multi-strand wires (as shown) or helical single-strand wires, and there may be one or more wires in each cable. The polymer encapsulant is essential to insulate the exposed wires where they are joined to the pins of the feed-throughs: to be an effective insulator, the encapsulant must remain bonded to the enclosure and the feed-through.

1.6 HERMETIC PACKAGES

This section and the following describe technology that was developed prior to the first modern implants (Figure 1.2). The important features of almost all commercial implants since 1970 are shown in Box 1.2. This design, with a weld-sealed titanium enclosure and feed-throughs, soon became the norm despite the fact that even in 1970 there were clearly other possible methods using ceramics, glasses and polymers. In the following sections, we describe the wide range of technology which was then available.

The hermetic package is an impermeable enclosure which, by acting as a barrier to water vapour, maintains the electronic components inside in a dry environment. The origins of this technology are in vacuum science: the feasibility of sealing electrical connections into evacuated glass vessels was demonstrated throughout the 20th century by incandescent lights bulbs and later electronic vacuum valves (tubes).

Figure 1.2 The first modern pacemaker was made by Telectronics in 1971. The engineer David Cowdrey, who had been charged with developing a hermetic enclosure, selected Ti because of its light weight, strength, corrosion resistance and weldability. He used deep-drawn Ti half-cases that were welded together using TIG welding to keep the inside cool. He also developed ceramic/Ti alloy feed-throughs for the package. Interestingly, the technology was never patented because the company's patent attorney advised them that it "was obvious"! This picture shows a Telectronics 'Slimline' device from 1977.

1.6.1 Vacuum methods

The earliest known apparatus for creating a vacuum was made by Berti in 1641: an 11 metre long-vertical tube was filled with water before taps at the top and bottom were shut and opened respectively, allowing the water to descend, evacuating the top of the tube. von Guericke started working on reciprocating pumps in the same decade, which enabled him to evacuate a barrel and later pairs of hemisphere to demonstrate the existence of air pressure. Boyle and Hooke improved the pump and added a manometer in 1658/9, so we know that they achieved a pressure of 6 Torr. Little progress was made in the next two centuries: the first prize for vacuum pumps at the Great Exhibition in London in 1851 went to Newman, whose pump only reached 0.5 Torr. However, in the remainder of the 19th century, progress was rapid, mainly due to pumps with liquid pistons, the lowest pressure reaching less than 10^{-5} Torr. McLeod invented his vacuum gauge in 1874, allowing pressures down to 10^{-4} Torr to be measured. The diffusion pump which was independently invented by Gaede in Germany and by Langmuir in the United States during the First World War, produced even lower pressures, the ultimate being 10^{-8} Torr until the 1950s. The need to mass produce evacuated light bulbs from the 1870s meant that vacuum pumps had to be made for

industrial use, with much higher pumping rates as well as low ultimate vacua. The Edison Company used manual pumps at first, but by the end of the 19th century mechanical pumps were in use. Methods for measuring low pressures were the subject of much work and by 1920 the minimum measurable pressure had reached 10^{-8} Torr[4].

1.6.2 Welding[5]

Before the late 19th century, blacksmiths had joined metals by hammering the hot parts, forming what might now be called a solid-state weld. The development of modern industrial processes started with the development of the oxy-hydrogen torch and then the hotter oxy-acetylene torch by Fouch and Picard, which was being used for commercial welding in 1903. Electric arc welding soon followed and joints were improved following the invention of the coated electrode by Kjellberg (patented in 1908), which kept atmospheric oxygen and nitrogen away from the molten metal, preventing brittleness and porosity in steel. Many other types of welding soon followed. In 1914, a 34-mile-long oxyacetylene-welded pipeline was fabricated in Oklahoma for the oil industry. Radiographic inspection of welded joints was first described in a paper from the US Naval Research Laboratory in 1926. In the same year, the first thick-walled pressure vessel was fabricated by welding. British shipbuilders made the first all-welded warship in 1923 and the first all-welded submarine in 1943, as welds were shown to be superior to rivets. Thus welding was well established by 1970 and not only could many alloys be joined in this way but evidently gas-tight or waterproof joints were possible. By that date, there was already literature on titanium welding and how to avoid porous joints. Titanium, and similar metals like tantalum, have the advantage that they are protected from corrosion by stable surface passivating films but at elevated temperatures they absorb atmospheric gasses and alter their properties, making them more brittle and possibly leading to porosity. However, if welding is done under inert gas or in a vacuum, strong gas-tight joints are possible. A thorough description of the metallurgy and welding methods for titanium and other metals can be found in Kearns (1984).

1.6.3 Glass

Glass technology is very ancient. Glass vessels and glazed pottery appeared early in human history. The material has been of great importance in science due to its useful properties, particularly transparency, impermeability and the fact that it can easily be shaped at high temperatures to form glassware, including chemical glassware. Macfarlane and Martin (2004) suggested that over half the most important experiments in the history of science would have been impossible without glass.

Glasses are supercooled liquids that lack long-range order; they are metastable and crystallisation rates may be negligible on a human time scale. Because there is

[4]This paragraph is based on (Redhead, undated).
[5]This paragraph is based on *(The History of Welding, undated)*

no change of state when they are cooled from a temperature at which they are liquid to room temperature, they are characterised by their progressive change in viscosity with temperature. Most glasses are mixtures of oxides and are categorised first by the major oxide constituent, the three most significant being silicate, phosphate or borate. Silicate glasses are by far the most important and only silicate has any technological value without admixed oxides, in the form of vitreous silica or "Fused Quartz", the others being too soluble in water.

Forming a joint between glass and metallic electrical conductors has been an important technological problem, at least since the mid-19th century experiments on ionisation of gasses. If a metallic wire is fused into the glass while it is softened by heating, and then allowed to cool, the glass is likely to crack unless the thermal expansion curves of the two materials are well-matched. Figure 1.3, taken from a book published for experimentalists in 1938, shows expansion curves for some relevant materials. Platinum had long been used to make seals to soda-lime glass, their Temperature Coefficients of Expansion (TCE) being close enough at 9.1×10^{-6} and 9.2×10^{-6} (Corning G8, "Soft Glass"). The thermal match between *Pyrex* (3.2×10^{-6}, "Hard Glass"), a borosilicate commonly used for chemical glassware, and tungsten (4.7×10^{-6}) is not ideal, but vacuum-tight joints are usually possible with wires under 1.5 mm diameter. If the wire is larger, a bead of *Nonex* glass (3.6×10^{-6}) was fused to the wire first and then this was joined to the *Pyrex* wall. Generally, metals with high TCE, like copper, cannot be joined to Hard Glasses but in the 1920s, Housekeeper (1923) showed that certain designs of joint could form satisfactory seals with copper. In one such case, the wires were flattened where they passed through the glass, a design often visible in incandescent light bulbs. Also in the 1920s, the American company Westinghouse developed iron-nickel-cobalt alloys that were well-matched to certain borosilicate glasses. *Fernico* is shown in Figure 1.3, but *Kovar* is now better known and became the standard alloy for making metal packages with glass feed-throughs, such as those shown in Figure 1.5(a). Figure 1.4 shows a hermetically-packaged device with metal-in-glass feed-throughs; it is a military device which illustrates the most advanced technology of that time.

1.6.4 Glass ceramics and solder glasses

The range of electrical conductors which could be used in TCE-matched feed-throughs was greatly increased by the development of glass-ceramics, which started from the discovery by Stookey at the Corning Glass Works just after the Second World War. He found that glasses in which a small amount of gold had been precipitated could then be converted to ceramic (devitrified) in a relatively short heat treatment, the gold acting as nucleation sites. Subsequent research (McMillan 1979) found that these *glass-ceramics* could be stronger than the original glass and have higher softening temperatures, allowing further high-temperature processing without distortion. Furthermore, these materials, which are often lithium-silicate mixtures with one other oxide, such as Pb, Zn or Al, can have TCE values from more than 15×10^{-6} to -3.9×10^{-6}, a range which includes all the metallic conductors that are of interest for implanted devices.

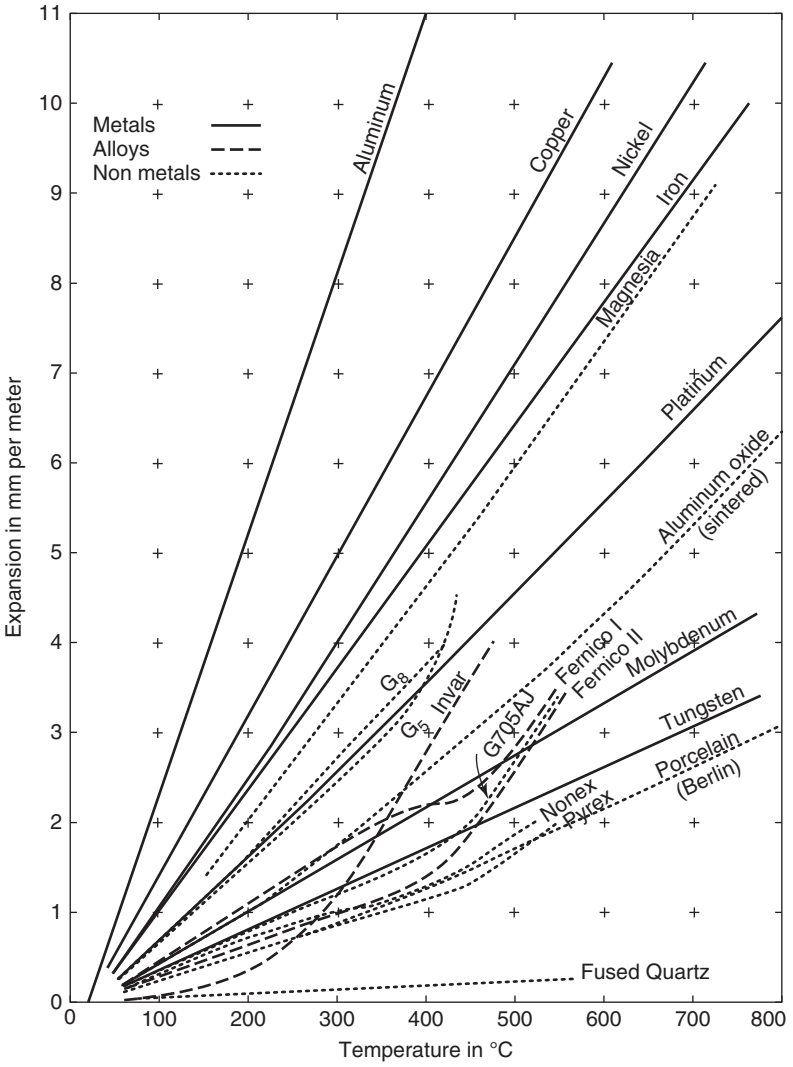


Figure 1.3 Thermal expansion curves for some metals, some special alloys, some ceramics and a few glasses, taken from Strong (1938). The broken lines are the insulators.

So-called solder glasses have been used for much longer. These are glasses that can be worked at moderate temperature, often about 500°C, and can be used for joining metal or ceramic or indeed other glasses. A package formed in this way is shown in Figure 1.5(b). They also need to have matched TCE, and since TCE and softening temperature are generally inversely related, it follows that they must be unusual glasses. They are sometimes not silicate but borate glasses, particularly lead borate. They may remain entirely vitreous or they may devitrify after making the joint; the

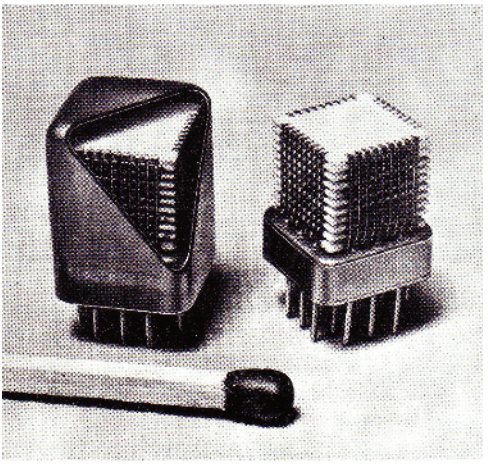
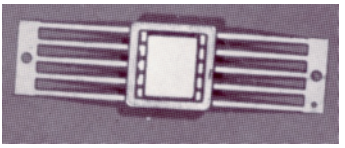
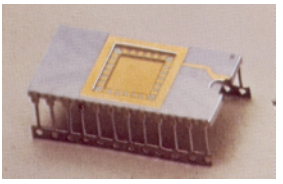


Figure 1.4 High-reliability microelectronic module (aerospace) taken from Manfield (1969). The package has metal-in-glass feed-throughs and is sealed by electron beam welding.

(a) Kovar package with metal-in-glass feed-throughs. The Kovar is gold-plated; lid usually resistance-welded to wall.



(b) Flat-Pack with alumina base and Kovar lead frame and seal ring. The side wall is solder glass. The metal beams of the lead frame pass through the side wall.



(c) Ceramic dual-in-line package made by co-firing three layers of alumina with tungsten metallisation, then brazing the lead frame outside and gold plating.

Figure 1.5 Three types of package that were available in the 1970s, showing that several technologies were available that might be suitable for hermetic packages for implants.

latter are sometimes called solder glass ceramics. Since TCE and solubility tend to be correlated, in some applications solder glasses may dissolve too quickly if exposed to moisture. A comprehensive review of solder glasses was published by Frieser (1975). They are significant materials for implant designers because they may allow hermetic seals to be formed that are not electrical conductors and therefore will not affect magnetic fields.

1.6.5 Ceramics

An alternative approach to making vacuum-tight joints between conductors and insulators is to metallise ceramics. The first method of metallisation was developed in

Germany during the Second World War: a molybdenum layer is applied by heating the ceramic to around 1500°C in a reducing atmosphere. The molybdenum starts as a powder, often mixed with some manganese. After metallising high-alumina ceramic in this way, a brazed joint can be made to the metal using Ag/Cu eutectic after plating the moly-manganese with nickel. This process was widely used in the ceramics industry by 1970 (Twentyman 1975).

As transistors became available in the 1950s, there was widespread interest in how to reduce the size of electronic assemblies and in 1958, the US Army set an objective to reduce sizes of military radio equipment ten-fold. The result has been described by Stetson (1986), who was one of the team at RCA to work on the contract. They made two breakthroughs: Gyurk developed the method for laminating metallised *green* (pre-sintered) ceramic sheets to make ceramic chip capacitors (1959) and Stetson himself invented the method for making three-dimensional circuits by punching holes to form vias (vertical connection between layers of metallisation) before metallising and laminating the green sheets (1960). With tungsten metallisation and alumina ceramic, the structure can be tough and impermeable to water vapour and gases, and was used to form high-reliability hermetic packages, such as that shown in Figure 1.5(c). In such a structure, the feed-throughs from the cavity inside to the connections outside can be part of the interconnection for the internal components. This is known as co-fired ceramic technology.

1.6.6 Microcircuit technologies

The microelectronics industry wanted to be able make multilayer circuits at lower temperatures than the moly-manganese process, because such a high processing temperature was neither convenient nor appropriate for forming resistors, capacitors or inductors. A technology that is usually called “thick film” was developed in which the metals were noble, so that they could be heated in air without oxidising, and these were fused to a ceramic substrate using a glass frit (powder). This technology originated from the need to make radio fuses for mortar shells in the Second World War, the circuit having to withstand the forces of acceleration at 10 000 g (Stetson 1986). The metal and glass mixture was screen printed with an organic vehicle which was then burnt off before sintering the mixture in place, usually at about 900°C. Dielectric layers of glass or devitrifying glass and higher resistivity materials could also be deposited so that by repeated printing and firing, a circuit could be built up. This process became attractive with the invention of transistors and later integrated circuits, as dice could be connected to the thick film circuit, achieving small, light and reliable devices. The technology was being developed in the 1960s. It was not originally a method for making seals but nevertheless, a soldered joint made to thick film metallisation may be vacuum-tight.

For completeness, we will mention the third method of metallisation which is thin film. Where thick films are typically 20 microns thick, thin film metallisation is under 1 micron. Early thin films were usually deposited by evaporation or sputtering in a vacuum. These films were not used for making seals, being too thin for brazing or soldering and generally not having adequate adhesion to the substrate.

1.6.7 Leak testing

These new glass and ceramic technologies for the formation of feed-throughs in hermetic packages could only be shown to be effective in a practical time if some method of measuring the gas leak rate was available. Fortunately, a method became available by this time; it was the use of mass spectrometers tuned to helium, generally known as *Helium Leak Testing.* Investigations in the 19th century into currents (rays) in discharge (vacuum) tubes found that there were both anode rays (ions) and cathode rays (electrons). At the end of the century, the cathode rays were more mysterious, because no particles smaller than atoms were expected. In 1886, Goldstein showed that the anode rays could be deflected by a magnetic field and by 1913, J.J. Thomson had shown that neon appeared to be composed of two isotopes of different mass. In 1919, his student F.W. Aston (1919), described the first mass spectrometer and listed the isotopes present in six elements, leading to instruments for analysis of elements. During the Second World War, the Manhattan Project required a method to show that containment vessels were gas-tight, to ensure that uranium hexafluoride would not escape, and a special mass spectrometer was designed (Nerkan 1991). This instrument was tuned to helium, because atoms of that gas are very small, penetrating the smallest crack, and its concentration in the atmosphere is low, so the background signal is small. It was described by Nier *et al.* in 1947 and industrial instruments were produced immediately after the war for the electrical industry. According to Hilleret (1999), sensitivity has increased from 10^{-7} Pa.m^3.s^{-1} in 1946 to 10^{-10} in 1970 and 10^{-13} in 1999[6].

To summarise, by 1970 many electrical components such as diodes, transistors and electrolytic capacitors were mass produced in hermetic enclosures. Glasses and glass-ceramics were available which allowed matched thermal expansion to all technologically-useful metals and alloys so that metallic packages could be made with metal-in-insulator feed-throughs. Furthermore, packages which were largely ceramic were available in several configurations, some of which had large cavities like pacemaker packages. Helium leak testing was already a standard method for quality assurance, and the relationship between helium leakage from the package and water vapour ingress into the package was known (Davey 1975).

1.7 ENCAPSULATION (ELECTRICAL INSULATION)

1.7.1 Insulation

Early in the 18th century, Gray discovered that materials can be classified as electrical conductors or electrical insulators (Mendenhall 1895) and this led to new demonstrations of electrical effects. Gray himself showed that a human body, a boy suspended by silk threads, could be charged with a friction generator and later discharged by drawing a spark. Even more spectacular were demonstrations by Nollet that electricity could be passed by chains of up to 600 people (200 monks on one occasion) before

[6] 1 Pa.m^3.s^{-1} is approximately 10 at.cc/s, which has been the familiar unit of leak rate.

allowing a spark jump to the ground (Fara 2002). Friction machines were used to generate electricity throughout that century and some technical progress was made. It is well-known that Franklin was active in electrical science, showing that lightning is an electrical discharge and making a practical electrostatic motor.

The quality of insulation became a critical matter early in the 19th century, following Oersted's discovery that an electric current can cause a magnetic needle to deflect (1820). This led would-be inventors in many countries to try to develop electric telegraph systems. The system that became most popular was that of Morse. For his first experimental telegraph line, from Washington to Baltimore, he buried the wire (Mendenhall 1895), but he abandoned this method because too much current leaked through the insulation and so he changed to the system common in Europe, which had first been used by O'Shaughnessy in Calcutta in 1839, of suspending the wires from insulators on poles. This avoided the need for good insulation of the wires.

1.7.2 Underwater insulation

The desire to lay telegraph cables under rivers meant that the need for better insulation could no longer be avoided. Fibres including cotton and hemp, impregnated with tar and other materials, were tested but none lasted longer than a few days. Fortunately, a British surgeon, stationed in Singapore, experimented with a material made from the sap of the Gutta Percha tree, which he found suitable for making splints. He sent specimens to London in 1822, where its properties of elasticity and good insulation were soon recognized. Unlike natural latex, this rubbery material is thermo-softening and becomes sticky when hot, so it could be extruded around the wires to form an insulating sheath (Routledge 1881). This timely discovery allowed a successful telegraph cable to be laid across the Hudson River in 1848 and the English Channel in 1850. Each copper wire was coated in Gutta Percha, before these wires were spun into a rope impregnated with tarred hemp and then protected by outer wires of iron. The first cable to be laid across the Atlantic did not last long because its insulation was damaged by high voltages (500 V) being applied, but it demonstrated the feasibility of the idea in 1858 and the first successful cable operated after 1865. A description of this cable technology from 1915 describes the copper core being coated with what we might call an adhesion promoter called *Chatterton's Compound* before the Gutta Percha extrusion (Anon 1915). The operating voltage was limited to 60.

Here we see the essentials of a successful underwater insulator or encapsulant: it must be flexible (like rubber) so that it can deform as necessary in service without rupture; it must have a sufficient volume resistivity; and it must adhere to the conductor so that water, which will diffuse through the permeable encapsulant, cannot form a layer of moisture at the interface. Any moisture allows corrosion of metals, dissolution of non-metals like solder glasses, and leakage currents to flow between conductors at different potentials.

1.7.3 Silicones

Major advances in insulation materials were made by industrial chemists at the American companies, Corning Glass and General Electric; the story has been very well told

by one of the major contributors (Rochow 1987). There were parallel developments behind the Iron Curtain. The problem was to try to find insulation that could withstand higher temperatures, above 125°C, allowing better electrical machinery. It was understood that it is the carbon chains in natural rubbers which were susceptible to oxidation. Kipping had shown that the silicon analogues of alcohols (silanols) are much less stable than their carbon counterparts, so that, for example:

$$2\,R_3SiOH \rightarrow R_3SiOSiR_3 + H_2O \tag{1.1}$$

condensation occurred, forming longer molecules. Di-silanols, molecules with two –OH groups, are capable of polymerisation and the –Si-O-Si–, siloxane structure, was often a product in silicon chemistry. When Franklin-Hyde at Corning was working on flexible binders that hold glass fibres together at temperatures over 125°C, he remembered that Kipping had described glue-like substances that formed from di-phenyl di-silanols. He succeeded in synthesizing silicones with phenyl and ethyl side groups. When heated to 200°C, the ethyl groups were oxidised, cross-linking and curing the material to form a resin varnish that withstood 180°C. This discovery led to the formation of the Dow Corning company in 1943. Rochow made two major contributions. First, he foresaw that the most promising structure for high service temperature would be one that minimised the number of carbon atoms on the silicon-oxygen backbone, which suggested a material that had never previously been synthesised, di-methyl

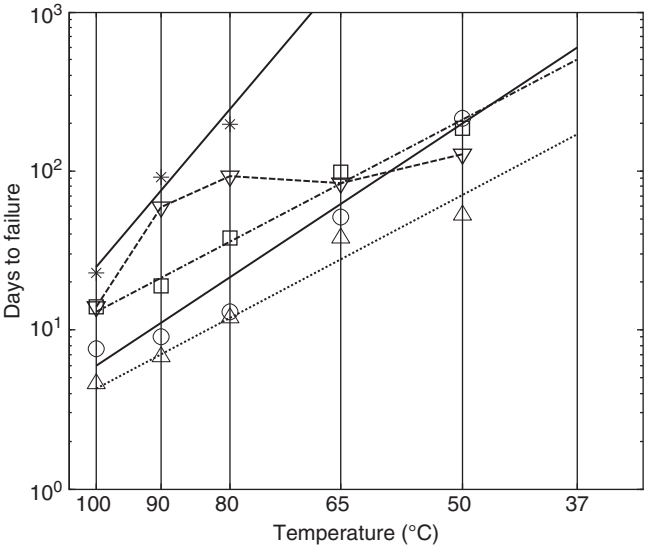


Figure 1.6 Arrhenius plot for accelerated adhesive life tests, replotted from Donaldson (1982). Adhesive is Dow Corning 3140, an alcohol-evolving RTV. The substrates are alumina (*), tin-lead solder (□), kovar (∇), copper-nickel alloy (○), oxidised titanium (Δ). Bonds to alumina are easily superior to all others.

silicone. Initially he synthesised this material using the expensive Grignard process, but later he invented a direct method of making chlorosilanes directly from silicon which was then hydrolysed to form the silanol that polymerised by condensation to form the poly di-methyl siloxane (PDMS or silicone). Direct synthesis is the basis of the modern silicone industry. Box 1.3 describes further processing to form practically useful silicone rubbers.

Box 1.3 Making practical silicones

Two major steps were necessary to obtain useful silicone rubbers. Methods had to be found to achieve very long chains, but with enough cross-links to hold them together. Two common methods are:

(i) The siloxane chains include some vinyl groups and some hydrogen in place of methyl groups. An addition reaction can occur between the Si-H and Si-CH=CH_2 to form a cross-link of Si-CH_2-CH_2-Si . This is catalysed by platinum and takes place with heating to moderate temperatures.

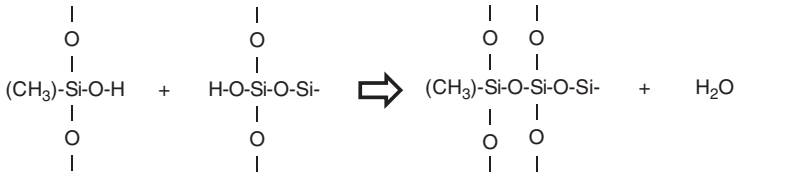
(ii) *Room Temperature Vulcanizing* (RTV) is an older method in which there are hydroxyl side groups and acyloxy side groups. When exposed to moist air, the water allows cross-linking:

$$\begin{aligned} &\text{–Si(CH}_3\text{)}_2\text{–OH} \; + \; \text{Ac–O–Si(CH}_3\text{)}_2\text{–} \\ &\rightarrow \; \text{–Si(CH}_3\text{)}_2\text{–O} - \text{Si(CH}_3\text{)}_2 - \; + \text{AcOH} \end{aligned} \tag{1.2}$$

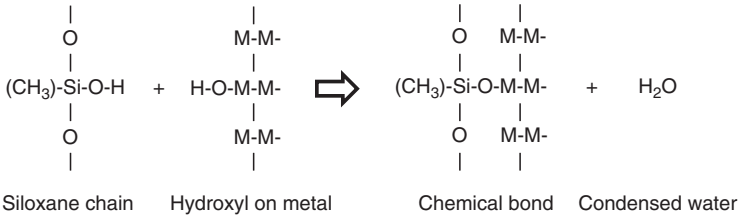
in this case, evolving acetic acid AcOH, but some evolve alcohols (Arkles and Redinger 1983).

The second major step was the incorporation of a filler to which the chains bond. Most commonly this is achieved with fumed silica, which has a similar atomic structure to the PDMS. However, the silica would soon be covered with water molecules, making the surface unavailable for bonding, so it is pre-exposed at high temperature to small cyclic siloxanes. It is these two steps that give us the rubbers that are strong, can stretch by 300%, and are stable above autoclave temperatures (134°C).

This inertness and purity made these attractive implantable materials (Box 1.5), but perhaps their most useful feature of the Room Temperature Vulcanizing (RTV) silicone (Box 1.3) is one that is hardly acknowledged by the manufacturers – long-term adhesion in the presence of water, as shown in Figure 1.6 (Gajewski 1983). The mechanism of cross-linking in the RTV types always involves bond formation with a silanol group on one chain and it seems likely that the hydroxyl group can form bonds to the surface of oxides, including glass, silica and ceramics. For example, bonding to silicate glass:



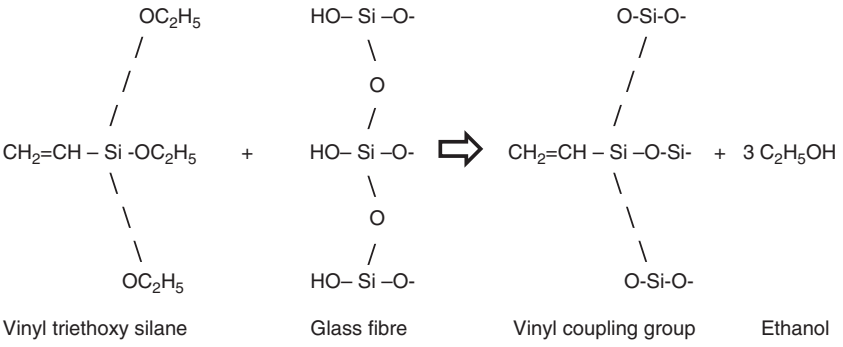
or on a metal surface:



The nature of the bond between the oxygen and the metal has been a matter of scientific enquiry (Pluedermann 1982). This is fundamental to neural prostheses, because the insulation relies on the durability of the adhesive bonds.

1.7.4 Primers

The stability of the bond formed when the silanol group meets an oxide surface has had other applications besides the bonding of silicone polymers to other materials. The problem of making strong composites by including glass fibres in a resin matrix presented itself after the Second World War. In 1947, a report to the US Navy showed that the application of a coating of triethoxy silane on glass fibres before impregnating them in polyester resin, dramatically reduced the effect of boiling water on the strength of the composite (Pluedderman 1982). Glass fibres were treated by silanes that bonded to the hydrophilic surface of the glass and presented organic groups to which the resin could bond.



The remaining double bond in the vinyl groups allows it to be incorporated into the polymer as it cures against the surface. This is the treatment that allows the long life of fibreglass boats in water and printed circuit boards in moist environments (Rochow 1987). This research was done in the 1960s in the USA. There are many silane coupling agents from which primers can be chosen to improve bonds between organic polymers (e.g. encapsulants), and the parts to which they should bond (Plueddermann 1982). This is relevant to high-modulus encapsulants (Box 1.4).

Box 1.4 High-modulus encapsulants

The use of low-modulus silicone rubbers makes the shape of the parts to be insulated and the control of the encapsulation process less critical. That simplification reduces the amount of development needed and is particularly helpful for experimental devices being made quickly without much engineering effort. High-modulus encapsulants like epoxy resins are normally used for pacemakers and structurally similar devices (Box 1.2). The resin forms the socket for the electrode lead, as well as insulating the connections at the feed-throughs and the wires running from there to the socket. The encapsulant must be stiff to support these conductors and prevent fracture due to forces applied after implantation (Figure Box 4a and 4b). The design and the encapsulation process should be developed so that nowhere during manufacture or service is the interfacial stress higher than the adhesive strength. As the adhesive strength declines as the joint is hydrolysed, the considerations should include the possible use of primers to diminish the rate of hydrolysis.

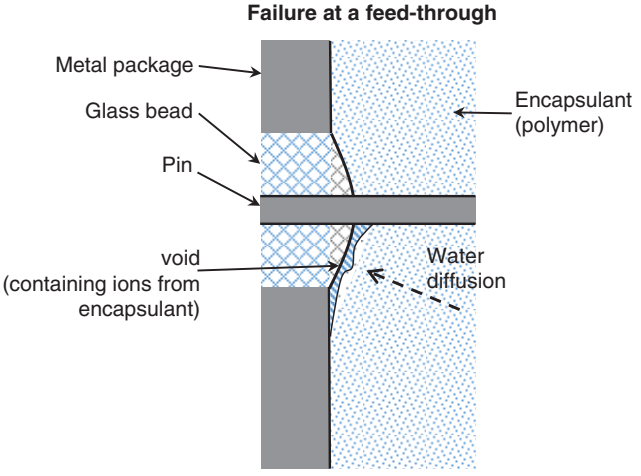


Figure Box 4a The void on the surface of the glass bead of the feed-through fills with water that diffuses through the encapsulant. Soluble salts that are residues left after inadequate cleaning, or that are present in the encapsulant, dissolve in the water and increase its conductivity. Failures like this are often made visible because of corrosion products from the metals.

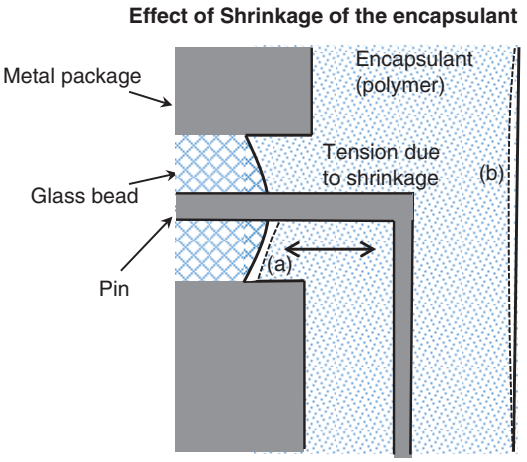


Figure Box 4b This diagram illustrates the disadvantage of using a high-modulus encapsulant if it will have any cause to shrink, for example due to cooling after cure. With this feed-through, which has a recessed glass bead, shrinkage sets up tension in the direction shown, tending to cause adhesion failure (a). This is exactly where adhesion is vital to prevent electrical leakage. Soft encapsulants are more likely to be able to relieve the tension by distortion at a free surface (b).

Box 1.5 Other important favourable properties of silicone rubbers as encapsulants

Besides the hydrolytic stability of their adhesive joints, many silicone rubbers have several other important properties.

(i) *Low Ionic Content:* Perhaps, because of the way they are manufactured from silicon via gaseous methyl silicon chlorides in the Direct Synthesis process, silicones have little contamination. Of particular importance is the low contamination by salts that would ionise so that concentrations of common ions like Na^+ and Cl^- are usually around 1 p.p.m. The epoxies used in earlier implants contained much more Na^+ and Cl^- than this, which probably partly explains why they failed so readily. Figure Box 4b shows the usual failure mode in early pacemakers with epoxy encapsulant. A void would form at the interface between the encapsulant and the package or component. The void might have been due to an absence of adhesion after curing the encapsulation, or was perhaps a bubble; alternatively, although there was initial adhesion, the stresses built up as the implant cooled after curing exceeded the strength of the adhesive joint and the materials parted. Either way, after implantation, water vapour will diffuse through the encapsulant and condense in the void. If that liquid is pure water, which has a

very high resistivity, the current flowing through it will be so small that the function of the implant is not compromised. Gas is likely to evolve at the conductors that have become electrodes under the encapsulant but if the current is small, the gassing rate may be slow enough for the gas to diffuse away harmlessly. If, on the other hand, the encapsulant has a relatively high concentration of salt impurities, some of these ions will dissolve in the water film, increasing the leakage current and the gassing rate. Rapid gas evolution will create high pressure, tending to lift off the encapsulant, and typically this tears the encapsulant away from the surface, extending the initial void. This type of runaway failure is exacerbated by encapsulants with high levels of ionic impurity and this has been one advantage of using silicones.

(ii) *Low Modulus and Low Cure Temperature:* The volume of the encapsulant will change: if it is cured at elevated temperature and then cools; if it is sterilised by autoclave; and when water diffuses into the encapsulant after implantation. This strain builds up stresses according to the modulus of the encapsulant and the shapes involved. Figure Box 4b shows an example where this effect caused failures on the glass bead of the feed-through, just where insulation is most important. This type of feed-through with deeply-recessed beads makes successful encapsulation very difficult. In general, the outside of the package should be convex, as far as possible, so that tension in the encapsulant presses the encapsulant against the surface. Although the bulk modulus of silicone rubbers is high, their low Young's Modulus, compared to resins like epoxy, means that distortion of the shape can usually relieve the low internal pressure due to volume shrinkage (Donaldson 1977).

(iii) *Transparency:* In order to inspect the encapsulation, it is convenient if the material is transparent. Some silicones are nearly ideal in this respect; for example, Nusil MED-6215, but this is an unfilled rubber and its extension-to-failure is only 80%. Most rubbers are filled and will not fail until hundreds of percent extension, so they are tougher and therefore more suitable for most implanted devices. This improvement is achieved by including silica filler, but this carries the disadvantage that the material is slightly cloudy so less detail can be seen by inspection.

1.8 EARLY IMPLANTED DEVICES

There were some early pacemakers that, like the animal stimulator of Louks (1933), had a coil into which current was induced, connected directly to the stimulating electrodes[7], but tuning the primary and secondary coils improves efficiency and allows

[7] See Exhibit A6002.73 in the Medical Collection, Science Museum, London.

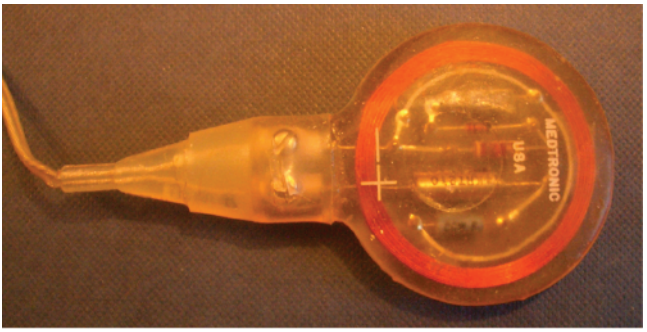


Figure 1.7 Dorsal column stimulator made by Medtronic from 1968–1978.

a smaller size coil if a radio frequency carrier is used. Such an inductively-coupled tuned-coil stimulator is shown in Figure 1.7.

Inductive-powering is advantageous because no battery is required in the implant, which means that it may be smaller in volume, and its life will not be limited by the battery capacity. Devices can be designed to which power and stimulation commands are sent together over one pair of coils. These have been very successfully used, particularly in cochlear implants for the deaf. A review of this technology was presented by Patrick *et al.* (1990). The small size of modern cochlear implants has allowed them to be implanted into pre-lingual infants enabling them to learn spoken language. However, continuous inductive powering does require a power transmitter to be held in place during use: this may be inconvenient or seen as unattractive.

Pacemakers[8] must be continuously active for life support and from the beginning it was seen as necessary that the implant should be battery-powered. But this requirement presented designers with a difficult challenge, because the electromotive force of the battery was continuously present, unlike inductive stimulators, like that shown in Figure 1.7, in which pulses are usually less than 1 ms duration with a low duty cycle (perhaps 1/50) and there is no voltage difference to drive destructive reactions at all while the device is not in use (except galvanic potentials between metal couples). In the earliest pacemakers, all the components were encapsulated in polymer (Figure 1.1 and Chardack *et al.* 1960). Figure 1.8 shows an intermediate design in which the electronic circuit was fabricated in thin film and then sealed in a metal enclosure with glass feed-throughs. At that time, the battery could not be included in the sealed package because these cells produced gas and could reach a pressure that might cause an explosion. Greatbatch solved this problem by developing the lithium iodide cell that did not gas, was inherently reliable, and could itself be hermetically-sealed (Greatbatch 1984). This led to the modern form of the implanted device that has replaced all others for pacemakers and is predominant for most other bionic devices that are implanted, the titanium package package with glass feed-throughs, containing the electronics

[8] History of Pacemakers, undated.

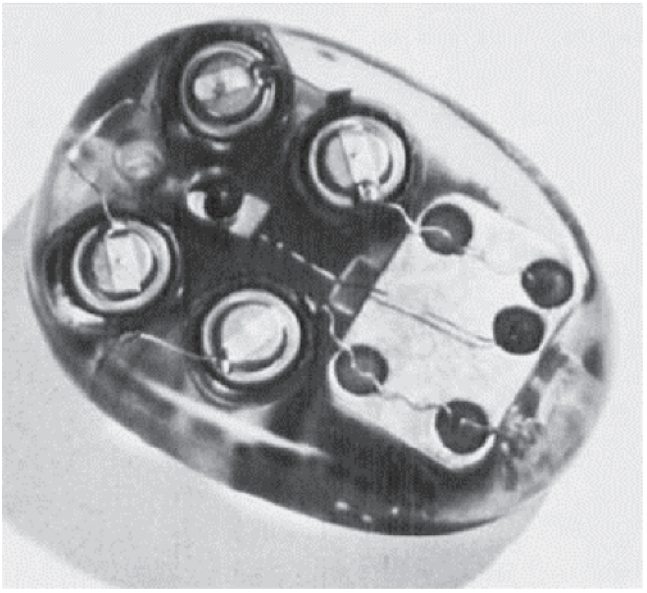


Figure 1.8 Intermediate design of pacemaker from Devices Implants Ltd. The hermetically-sealed package is on the right and the battery on the left, all encapsulated in epoxy resin (Kenny 1969). Figure with permission from the Annals of the New York Academy of Sciences.

and the battery, with some external insulation where the cable or connector is joined to the feed-throughs (Box 1.2). For stimulators such as this, the battery is inside the hermetic package and only pulses appear at the output cables which is much less demanding on the encapsulantion.

1.9 AFTERWORD

The development of implantable devices for medical application is at the intersection of neuroscience, clinical science and engineering. Although some justification for attempting new experimental procedures has been based on experiments on animals, supplemented by anatomical studies on human cadavers and experiments on human volunteers using imaging techniques, much of the justification has derived from observations made during treatment, some fortuitous, of patients who are injured or undergoing some surgical operation.

The treatment of patients by electricity is very ancient and in principle neuroprosthetic devices might have been attempted after Galvani and after Faraday's discovery of electromagnetic induction (Louks 1933), but implantation would not have been practical until after anaesthesia allowed prolonged surgery without extreme pain, and

Table 1.1 Packaging Methods discussed at Stanford Meeting in 1979

	Substrate	Package	Package Seal	Encapsulant
1	Thick Film Hybrid	Machinable ceramic	Epoxy	Not described
2	PCB	Copper	Solder	Not described
3	PCB	None	None	Wax
4	PCB	Stainless steel	Weld	Not described
5	Thick Film Hybrid	Kovar	Weld	Not described
6		Tantalum	Weld	Not described
7	Thick Film Hybrid	Ceramic	Epoxy	Epoxy
8	Thick Film Hybrid	Titanium	Weld	Parylene
9	Thin Film Hybrid	Glass	Solder	Epoxy
10	None	None	None	Silicone
11	None	None	None	Epoxy

aseptic techniques brought the risk of surgery down to an acceptable level. These techniques are the great contributions from the 19th century, but neuroscience was not then sufficiently advanced.

The key that opened the door for neuroprosthetic devices was the transistor and its arrival occurred when much more was known about the brain and nervous system than in the 19th century. We have shown that there were also many other lines of technological development which have been essential to success: in vacuum science, metallurgy, glass, ceramic and polymer technology and improved battery technology. Much of this know-how came from innovations in the USA, often driven by the Second World War or the Cold War. Nevertheless, in the 1970s, it was far from clear how to make reliable implants and researchers tried all sorts of methods, with far greater variety than we see now. For example, in a workshop held in Stanford in 1979 called "Implantable Transducers and Systems: Packaging Methods and Testing Criteria", the speakers described the types of implant construction shown in Table 1.1.

Dr Robert White from the host group described the major difficulties at that time (Hambrecht and Reswick, in McNeal 1977). "The packaging … and specifically the achievement of reliability against insulation breakdown, fluid seepage and lead breakage is perhaps the most widespread and common problem." However, after pacemaker batteries could be included inside the hermetic packages and with good choice of materials, design and quality control, the form of the pacemaker became established and this has been copied in most other types of device that have followed (Box 1.2). The industry has achieved significant reduction in size and increase in functionality as integrated circuits, programmable devices and now remote communication have been introduced. During this time, the form of the packaging has changed little, but that conventional design is now often increasingly inappropriate as new types of device have to be very small with many electrodes (e.g. retina stimulators). New types of hermetic micropackages are needed to fit in such small spaces and it

may be that it is better to dispense with the package entirely and rely on encapsulation of the integrated circuit (Vanhoestenburghe and Donaldson 2013). These new requirements should encourage innovation using available technology, some of which is new, such as Diamond-like Carbon films, but much is original, as described above, from the prehistoric period of bionics.

Box 1.6 The Medical Research Council, Neurological Prostheses Unit, 1968 –1992

One of us (G.S.B.) designed and built an implant to stimulate the visual cortex and this was implanted in a blind volunteer in 1967. Although the device was not reliable, it established the possibility that blind people might have implants to restore some sense of sight (Brindley and Lewin 1968). There are two bases for the visual prosthesis: the less important is the mapping of the visual field on the occipital cortex. This was discovered and its fine detail well established during the First World War by recording the visual field losses from wounds to the occipital poles of the hemispheres, mainly by the British neurologist Gordon Holmes. The more important base for the visual prosthesis was the electrical stimulation of the occipital cortex during operations to treat epilepsy, which occurred as a late effect of such wounds. This was done by German surgeons during the first few years after the First World War. Similar stimulation was done by Penfield in Montreal in the 1930s and 1940s, with apparently conflicting results. My decision to make the first visual prosthesis depended absolutely on my judging that the descriptions given by Foerster (1929) and Krause and Schum (1931) were accurate, and those given by Penfield substantially inaccurate.

I learned only in 1969 that the idea of stimulating the occipital cortex to provide artificial vision had already been suggested by Krieg (1953). I presented two Communications to the Physiological Society in 1964, one on the number of stimulation channels that should be necessary for reading (Brindley 1964a), and the other on the design of an array of radio-frequency transmitters and receivers that could be used to excite the implanted electrodes (Figure Box 6) (Brindley 1964b). The first implantation was done in 1967 (Brindley and Lewin 1967, 1968).

The British Medical Research Council established a research unit in 1968 so that further applications of the technology and methods could be developed, and new applications explored. The Chief Engineer from foundation to closure in 1992 was P.E.K. Donaldson, father of the first author.

A large number of methods were explored by Brindley and his many collaborators, which were reported for the 4-yearly reviews. It is interesting to see how many of these ideas were far-sighted and which have been found ineffective or been superseded.

Because of their historical interest, G.S.B. reviewed the 26 projects in the table to consider the extent to which each was based on clinical observation. The majority actually had no basis on clinical observation, but the following are either exceptions or are worth further description:

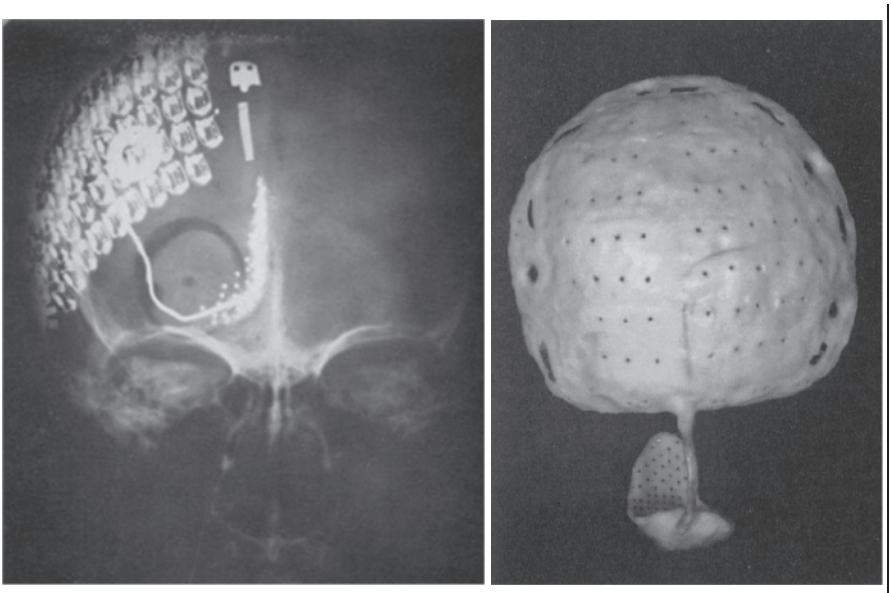


Figure Box 6 Eighty-channel visual prosthesis, implanted in a blind volunteer in 1967. The extracranial part of the device had 80 radio frequency receivers, each connected to one of the electrodes on the intracranial silicone cap that was implanted over the right occipital cortex. Thirty-nine channels produced phosphenes after implantation. The receivers and the electrodes are visible in the X-ray image (Brindley and Lewin 1968). Each receiver in the implant was encapsulated in epoxy resin before being inserted into the silicone cap. Failures were probably due to wire breakage since failures were never partial. Biocompatibility had previously been tested in baboons.

Table 1.2 Implanted Devices reported from the MRC Neurological Prostheses Unit

	Project	1974	1978	1982	1987
1	Artificial visual pathway (occipital cortex)	✓	✓	✓	✓
2	Auditory-tactile signalling	✓	✓		
3	Implantable bladder and sphincter controller (S3 –S4)	✓	✓	✓	✓
4	Artificial motor pathway (nowadays called a Brain-Computer Interface)	✓	✓	✓	✓
5	Artificial auditory pathway (cortex)	✓	✓		
6	Carotid sinus stimulator for hypertension	✓	✓	✓	
7	Denervated muscle stimulation	✓	✓		
8	Artificial sphincter (stress incontinence)	✓	✓	✓	✓
9	Flexible implantable lens to allow accommodation		✓		

Table 1.2 (***Continued***)

	Project	1974	1978	1982	1987
10	Cerebellar stimulator (epilepsy)		✓	✓	
11	Posterior column stimulator (multiple sclerosis)		✓		
12	Deep brain stimulation (pain relief)		✓		
13	Deep brain stimulation (auditory prosthesis)		✓		
14	Deep brain stimulation (obesity or anorexia nervosa)		✓	✓	
15	Stimulation for paraplegic walking		✓	✓	✓
16	Pancreatic stimulator (diabetes)			✓	
17	Stimulator for grasp			✓	
18	Intracranial pressure sensors			✓	✓
19	Conditional pudendal nerve stimulator (detrusor instability)			✓	✓
20	Intercostal nerve stimulator (tetraplegia)				✓
21	Artificial anal sphincter				✓
22	Deep brain stimulator for tremor (in MS)				✓
23	Hypogastric plexus stimulation for ejaculation (SCI)				✓
24	Cannula and reservoir for semen (SCI)				✓
25	Cochlear implant				✓
26	Facial nerve stimulator (UMN facial palsy)				✓

Not all of these of these projects are bionic; numbers 8, 9, 21 and 24 were not electrical in any way.

1. Clinical observation, in conjunction with post-mortem examination, showed that the retina was mapped on the visual cortex, and by 1918 the map was well-established and accurate. Without the map, Foerster and Krause would probably not have operated on their patients with occipital epileptic foci, and if they did operate, would not have stimulated. So for the visual prosthesis, three things were absolutely necessary: good clinical observation, post-mortem examination of the same patients, and the initiative taken independently by two German surgeons in different centres to stimulate the occipital lobes before removing them.
2. Clinical observation told us that people with defective hearing often do better with a tactile supplement, for example being able to touch the speaker's larynx. The details of the device depended slightly on clinical observation.
3. It is a clinical observation that a person with the spinal cord cut through at any level above S3 has no bladder control. This could also be deduced from the anatomy, but the deduction could, by an extreme sceptic, be deemed uncertain, whereas the observation, made by the patient himself, is certain. The design of the device owes nothing to clinical observation.

4 and 15. This project was about two kinds of implant: leg-muscle activators controlled by switches worked by the patient's fingers, and similar activators controlled by signals taken from the leg area of the motor cortex. The biological knowledge needed for the design of the leg-muscle activators is anatomical, and was derived about 96% from dissection, 2% from experiments on corpses, and 2% from experiments on live human volunteers. Decisions on how to use them were based mainly on clinical observation.

10. This project had, in my view, absolutely no scientific justification. A respected American neurosurgeon, Irving Cooper, decided on theoretical grounds that stimulation of the cerebellar cortex was likely to suppress epilepsy. He tried it, uncontrolled, on seven patients, and reported good results. The King's College Hospital neurologists read his paper, and asked me if I would help them try to replicate it. All the relevant clinicians concurred that the risks were very small, so I checked that the MRC Unit staff had no objections, and then consented. I based this project only on Cooper's clinical observations, which were weak because uncontrolled, but not negligible. I dismissed his original theoretical basis as entirely worthless. We made three stimulators. They were all implanted, and all three patients thought their fits had become fewer. Only one patient would consent to a blind trial. The trial showed that there was no effect whatever on the frequency of fits. The patient nevertheless continued to believe that the implant was doing her good, and continued to use it.

11. This project was also, in my opinion, based on dubious clinical observation, with no scientific justification whatever. Posterior column stimulators for pain relief work very well, but this was not for pain relief. We abandoned the project before we had wasted much time on it.

12. This project was based on a chance observation by an American neurosurgeon during stereotaxic surgery. The observation was wholly unexpected, and could well be classified as a clinical observation.

18. It was chiefly clinical observation that convinced neurosurgeons of the need to monitor intracranial pressure. The *design* of our sensors was influenced only slightly by clinical observation.

20. Needed the clinical observation that when both phrenic nerves are injured, the intercostal muscles, perhaps with some help from the sternomastoids, trapezius and platysma, can give adequate breathing, at least for a few hours.

26. It was from clinical observation that I decided that our patient was likely to gain benefit from a facial nerve stimulator. Clinical observation influenced the *design* only in that I respected the patient's wish that the stimulator be inconspicuous, and consulted him about details.

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